Disclosures

Dr. Wood has no financial conflicts of interest or disclosures.
**Cabotegravir and Rilpivirine**
Oral and Injectable Preparations

**Optional Lead-In Oral Components**
- Cabotegravir + Rilpivirine
  - Cabotegravir: 30 mg
  - Rilpivirine: 25 mg

**Intramuscular Injection Components**
- Cabotegravir + Rilpivirine
  - Cabotegravir: 200 mg/mL
  - Rilpivirine: 300 mg/mL
Cabotegravir and Rilpivirine Extended Release Injectable Suspension

Indications

- **Complete regimen to treat HIV-1**
- **For adults and adolescents (≥12 years who weigh ≥35 kg)**
  - Replace antiretroviral regimen in persons with HIV RNA <50 copies/mL
  - On stable antiretroviral regimen
  - No history of treatment failure
  - No known or suspected resistance to cabotegravir or rilpivirine
- **Oral Lead-In**
  - Lead-in is optional
- **Continuation Phase Injections**
  - Approved for every 1-month and every 2-month injections
  - Doses are different with every 1-month and every 2-month injections
  - Injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information
Schedule for Every 1-Month Injectable Cabotegravir and Rilpivirine

**Schedule for Injections**: One-time initiation phase injections then monthly continuation phase injections thereafter

Administer first injections on the last day of current fully suppressive antiretroviral therapy or last day of oral lead-in (if used)

### Optional Oral Lead-In

<table>
<thead>
<tr>
<th>Initiation Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Optional Oral Lead-In Dosing**: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

**Dosing for 1-time Initiation Phase Injections** = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

**Dosing for Continuation Phase Injections** = LA Cabotegravir (400 mg): 2 mL IM and Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site) injections may be given up to 7 days before or after the scheduled date

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD
### Management of Missed Injections in Persons on Every 1-Month Dosing

**Management for Planned and Unplanned Missed Injections in Patients on Every 1-Month Dosing**

<table>
<thead>
<tr>
<th>Time Since Last Injection</th>
<th>Recommendation for Oral Bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Planned Missed Injection</strong>&lt;br&gt;• Time to miss a scheduled injection &gt;7 days</td>
<td>• <strong>Two oral options are available:</strong>&lt;br&gt;- Take daily oral therapy with cabotegravir 30 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits.&lt;br&gt;- Take any fully suppressive antiretroviral regimen until injections resume&lt;br&gt;• Start oral therapy with either option above approximately 1 month (+/- 7 days) after the last injection dose of cabotegravir and rilpivirine.&lt;br&gt;• Continue oral therapy until the day injection dosing is restarted.</td>
</tr>
<tr>
<td><strong>Unplanned Missed Injection</strong>&lt;br&gt;• Time from last injections is &gt;1 month + 7 days</td>
<td>• If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate.</td>
</tr>
</tbody>
</table>

Source: Cabotegravir-Rilpivirine Prescribing Information
## Recommendations for Restarting Injection Doses after Missed Injections with Every 1-Month Dosing Schedule

<table>
<thead>
<tr>
<th>Time Since Last Injection</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 2 months</td>
<td>Resume with cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injections as soon as possible.</td>
</tr>
<tr>
<td>Greater than 2 months</td>
<td>Reinitiate with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) then continue to follow the monthly cabotegravir 400 mg (2 mL) and rilpivirine 600 mg (2 mL) monthly injection dosing schedule.</td>
</tr>
</tbody>
</table>

Source: Cabotegravir-Rilpivirine Prescribing Information
Schedule for Every 2-Month Injectable Cabotegravir and Rilpivirine

Schedule for Injections*: First two injections given 1 month apart then every 2 months thereafter

Administer first injections on the last day of current antiretroviral therapy or last day of oral lead-in (if used)

Optional Oral Lead-In
Initiation Phase
Continuation Phase

1 Month 1 Month 2 Months 2 Months 2 Months 2 Months…

Optional Oral Lead-In Dosing: Cabotegravir 30 mg PO daily and Rilpivirine 25 mg PO daily

*First Two Injections (Initiation Phase): given 1 month apart, before transitioning to every 2-month dosing

*Dosing for All Injections = LA Cabotegravir (600 mg): 3 mL IM and Rilpivirine (900 mg): 3 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Injections may be given up to 7 days before or after the scheduled date
## Oral Bridge Therapy for Planned and Unplanned Missed Injections in Patients on 2-Month Dosing

<table>
<thead>
<tr>
<th>Time Since Last Injection</th>
<th>Recommendation for Oral Bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Planned Missed Injection</strong></td>
<td>Two oral options are available:</td>
</tr>
</tbody>
</table>
| • Time to miss a scheduled injection >7 days |   - Take daily oral therapy with cabotegravir 50 mg plus rilpivirine 25 mg for up to 2 months to replace missed injection visits.  
   - Take any fully suppressive antiretroviral regimen until injections resume  
   • Start oral therapy with either option above approximately 2 months (+/- 7 days) after the last injection doses.  
   • Continue oral therapy until the day injection dosing is restarted. |
| **Unplanned Missed Injection** | If oral therapy has not been taken, reassess patients clinically to ensure resumption of injections remains appropriate. |
| • Time for scheduled injection is missed or delayed by >7 days |
## Recommendations for Restarting Injection Doses after Missed Injections with Every 2-Month Dosing Schedule

<table>
<thead>
<tr>
<th>Missed Injection Visit</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Injection 2**        | **Time since last injection ≤2 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible, then continue to follow the every-2-month injection dosing schedule.  
**Time since last injection >2 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue to follow the every-2-month injection dosing schedule thereafter. |
| **Injection 3 or Later** | **Time since last injection ≤3 months**: Resume with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) as soon as possible and continue with the every-2-month injection dosing schedule.  
**Time since last injection >3 months**: Re-initiate the patient with cabotegravir 600 mg (3 mL) and rilpivirine 900 mg (3 mL) followed by the second initiation injection dose 1 month later. Then continue with the every-2-month injection dosing schedule thereafter. |

Source: Cabotegravir-Rilpivirine Prescribing Information
Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 1-Month to Every 2-Month Cabotegravir and Rilpivirine

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)
Cabotegravir and Rilpivirine Extended-Release Injectable Suspension
Switching from Every 2-Month to Every 1-Month Cabotegravir and Rilpivirine

Every 2-Month Injections

2 Months

Every 1-Month Injections

1 Month

Switch

*Dosing for Every 2-Month Injections* = LA Cabotegravir (600 mg): 3 mL IM + Rilpivirine (900 mg): 3 mL IM

*Dosing for Every 1-Month Injections* = LA Cabotegravir (400 mg): 2 mL IM + Rilpivirine (600 mg): 2 mL IM

Injections of rilpivirine and cabotegravir given as 2 separate IM injections at separate gluteal sites (opposite sites or 2 cm apart on same site)

Source: Cabotegravir-Rilpivirine Prescribing Information; Illustration: David H. Spach, MD
Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance

ATLAS Study
Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Design

**Background:** Phase 3, randomized, open-label trial assessing IM cabotegravir plus IM rilpivirine after oral induction for adults taking a 3-drug oral antiretroviral therapy regimen

**Inclusion Criteria**
- Age ≥18 years
- Taking 2 NRTIs + INSTI, NNRTI, or PI
- Stable ARV regimen ≥6 months
- HIV RNA <50 copies/mL ≥6 months
- No history of virologic failure
- No INSTI or NNRTI resistance mutations allowed, except for K103N
- No chronic hepatitis B

<table>
<thead>
<tr>
<th>Lead-In</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral CAB + RPV</td>
<td>IM CAB + RPV every 4 weeks (n = 308)</td>
</tr>
<tr>
<td>Continue 3-drug Oral Antiretroviral Therapy (n = 308)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAB = cabotegravir; RPV = rilpivirine

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis

Long-Acting IM Cabotegravir and IM Rilpivirine for HIV Maintenance
ATLAS Study: Results

<table>
<thead>
<tr>
<th>Country, HIV-1 Subtype</th>
<th>At Baseline</th>
<th>At Virologic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INSTI RAMs</td>
<td>NNRTI RAMs</td>
</tr>
<tr>
<td>Russia, A/A1</td>
<td>L74I</td>
<td>E138E/A</td>
</tr>
<tr>
<td>F, France, AG</td>
<td>None</td>
<td>V108V/I, E138K</td>
</tr>
<tr>
<td>M, Russia, A/A1</td>
<td>L74I</td>
<td>None</td>
</tr>
</tbody>
</table>

There were also 4 virologic failures in the oral ART arm; new RAMs detected included one G190S, one M184I, and one M230M/I.

Abbreviations: RAMs = resistance associated mutations

### Injection Site Reactions (ISRs)

<table>
<thead>
<tr>
<th>Type of Reactions</th>
<th>Participants (%) with Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants who received injections, n</td>
<td>303</td>
</tr>
<tr>
<td>Any reaction, n (%)</td>
<td>250 (81)</td>
</tr>
<tr>
<td>Pain, n (%)</td>
<td>231 (75)</td>
</tr>
<tr>
<td>Grade 3 pain, n (%)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Pain leading to withdrawal</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Nodule, n (%)</td>
<td>37 (12)</td>
</tr>
<tr>
<td>Induration, n (%)</td>
<td>30 (10)</td>
</tr>
<tr>
<td>Swelling, n (%)</td>
<td>23 (7)</td>
</tr>
<tr>
<td>Median duration of reaction, days</td>
<td>3</td>
</tr>
</tbody>
</table>

The majority of ISRs (99%) were grade 1-2; 88% resolved within 7 days.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance

ATLAS-2M
**IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance**

**ATLAS-2M Study: Design**

- **Background**: Phase 3, randomized, open-label trial assessing IM CAB plus IM RPV maintenance ART administered every 8 weeks versus every 4 weeks.

- **Inclusion Criteria**
  - Age ≥18 years
  - Taking an uninterrupted first or second oral standard of care ART regimen for ≥6 months
  - HIV RNA <50 copies/mL ≥6 months at screening and >2x in prior year
  - No history of virologic failure
  - No INSTI or NNRTI resistance, except that K103N mutation allowed

### Lead-In

<table>
<thead>
<tr>
<th>Oral CAB + RPV</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections Every 8 weeks^</td>
<td></td>
</tr>
<tr>
<td>(n = 522)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral CAB + RPV</strong></td>
<td>CAB 400 mg (2 mL) + RPV 600 mg (2 mL) 2 mL IM Injections Every 4 weeks#</td>
</tr>
<tr>
<td>(n = 523)</td>
<td></td>
</tr>
</tbody>
</table>

*Some individuals enrolled from ATLAS trial; those already receiving IM CAB + RPV through ATLAS did not require oral lead-in for ATLAS-2M.

^Participants first received loading doses of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study weeks 4 and 8.

#Participants first received loading dose of CAB 600 mg (3 mL) + RPV 900 mg (3 mL) 3 mL IM injections given at study week 4.

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

Weeks 48: Virologic Response by FDA Snapshot Analysis

![Graph showing virologic response](image)

- HIV RNA <50 copies/mL (%)
- **94**
- **93**

HIV RNA ≥50 copies/mL at 48 weeks: 9/522 (2%) in q8-week arm, 5/523 (1%) in q4-week arm

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

<table>
<thead>
<tr>
<th></th>
<th>Total Number of Participants</th>
<th>Archived (Baseline) RPV RAMs*</th>
<th>Archived (Baseline) INSTI RAMs*</th>
<th>RPV RAMs Detected at Time of VF</th>
<th>INSTI RAMs Detected at Time of VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q8 Weeks</td>
<td>8</td>
<td>5/8</td>
<td>1/8</td>
<td>6/8</td>
<td>5/8</td>
</tr>
<tr>
<td>Q4 Weeks</td>
<td>2</td>
<td>0/2</td>
<td>0/2</td>
<td>1/2**</td>
<td>2/2</td>
</tr>
</tbody>
</table>

*Detected by archive (DNA) genotype
**One participant had RPV RAMs; the other an NNRTI polymorphism that reduced RPV activity >100-fold

Abbreviations: RAMs = resistance associated mutations; VF = virologic failure

IM Cabotegravir and IM Rilpivirine Every 2 Months for HIV Maintenance
ATLAS-2M Study: Results

<table>
<thead>
<tr>
<th>Types of Reactions</th>
<th>IM CAB + RPV Every 8 Weeks, n (%)</th>
<th>IM CAB + RPV Every 4 Weeks, n, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants who received injections, n</td>
<td>516</td>
<td>517</td>
</tr>
<tr>
<td>Any reaction, n (%)</td>
<td>392 (76)</td>
<td>390 (75)</td>
</tr>
<tr>
<td>Serious reaction, n (%)</td>
<td>1 (&lt;10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Reaction leading to discontinuation, n (%)</td>
<td>6 (1)</td>
<td>11 (2)</td>
</tr>
<tr>
<td>Pain, n (%)</td>
<td>371 (72)</td>
<td>363 (70)</td>
</tr>
<tr>
<td>Nodule, n (%)</td>
<td>54 (10)</td>
<td>89 (17)</td>
</tr>
<tr>
<td>Induration, n (%)</td>
<td>41 (8)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>Swelling, n (%)</td>
<td>32 (6)</td>
<td>27 (5)</td>
</tr>
</tbody>
</table>

*The majority of ISRs (98%) were grade 1-2.*

Long-Acting Cabotegravir-Rilpivirine Considerations if Adherence Challenges or Virologic Failure
“The panel recommends against long-acting, intramuscular CAB and RPV in people who have detectable viral load due to suboptimal adherence to ART and who have ongoing challenges with retention in HIV care, except in a clinical trial.” (AIII)

*HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV*
Long-Acting Cabotegravir-Rilpivirine (CAB-RPV) and Virologic Failure

- Guidelines previously recommended checking resistance assay(s) within 4 weeks ART stoppage
- Injectable CAB and RPV have very long half-lives
- Resistance tests now recommended with virologic failure after CAB-RPV stoppage, regardless of time since last dose

Source: HHS Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. Sept 21, 2022.
Summary

• Intramuscular cabotegravir-rilpivirine (CAB-RPV) is the first approved long-acting antiretroviral treatment regimen

• Eligible patients are those taking a stable oral regimen with suppressed HIV RNA, no HBV, no CAB or RPV resistance

• Must attend visits every 1 or 2 months for injections administered by a healthcare professional

• Usage has been limited thus far due to clinical factors, insurance coverage, and logistical barriers
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